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SPECIAL CONTRIBUTION

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Marijuana use in children: An update focusing on pediatric tetrahydrocannabinol and cannabidiol use

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Abstract

Cannabis is the most used recreational drug in the United States, and its use is increasing among children and adolescents. With the increase in legalized use, there have been increases in intentional and accidental cannabis exposure in the pediatric population. There is also minimized perceived risk. We review the current use of cannabis and its derivatives, the drug effects and clinical presentation, common misconceptions, pharmacology, and epidemiology. Finally, we review some long-term consequences of cannabis use.

KEYWORDS
cannabis, emergency medicine, pediatrics

1 | INTRODUCTION

Cannabis is the most used recreational drug in the United States, with increasing use by children and adolescents. Both intentional and accidental exposures of children and adolescents have increased, particularly in states with legalized use.[1] According to the Monitoring the Future data, up to 25% of high school seniors report using within the previous month.[2] Additionally, cannabis legalization has spread the perception of minimal risk and is associated with increased use.[1,3] In addition to risks from acute ingestion/intoxication, there is also significant potential for permanent neuropsychiatric changes with use in childhood. Physicians, parents, and children alike need to be aware of these risks.

2 | PHARMACOLOGY OF CANNABINOIDS

Cannabis has a variety of methods of delivery, including smoked/inhaled or ingested. Marijuana is a dried and crushed flower or leaf, whereas hashish is a resin and hash oil is a concentrated oil. Alternative forms of cannabis as well as electronic vapor use have added to accessibility as well as potency of the drug.[4,5] The chemical components of cannabis, known as cannabinoids, are responsible for exerting psychoactive and sedative effects after binding to specific

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receptors in the brain. The two best studied and well-known cannabinoids are cannabidiol (CBD) and δ-9 tetrahydrocannabinol (THC), although over 100 types of cannabinoids are known to exist.[5] A recent Centers for Disease Control and Prevention health advisory describes an increase in products appearing to be CBD and THC containing products with δ-8 tetrahydrocannabinol. This has similar effects to δ-9 tetrahydrocannabinol, but the product label can be misleading as it only reports the amount of the δ-9 THC.[6]

THC acts in the hypothalamus, cerebellum, and hippocampus, producing many of the psychotropic feelings and effects of cannabis. THC serum concentrations rise within minutes of ingestion with peak effects within 1–4 hours and then rapidly decline. THC is highly lipophilic and distributes into lipid rich tissues. It also undergoes oxidation to a biologically active metabolite: 11-hydroxy-THC, which undergoes hepatic metabolism. The final metabolite, THC-COOH, can be found in the urine 3–5 days after a single drug exposure.[7-9]

CBD is the other plant-derived cannabinoid commonly in use. First isolated in 1963, it does not bind to the same receptors as THC and lacks any psychoactive effects. CBD is used for many medicinal purposes due to reported analgesic, anti-epileptic, anti-nausea, antiemetic, anti-inflammatory, anxiolytic, antipsychotic, and anti-ischemic properties.[10] Currently the only Food and Drug Administration (FDA)-approved use is for certain epilepsy disorders. CBD containing products are often unregulated and have imprecise concentrations of CBD oil and may contain some THC.

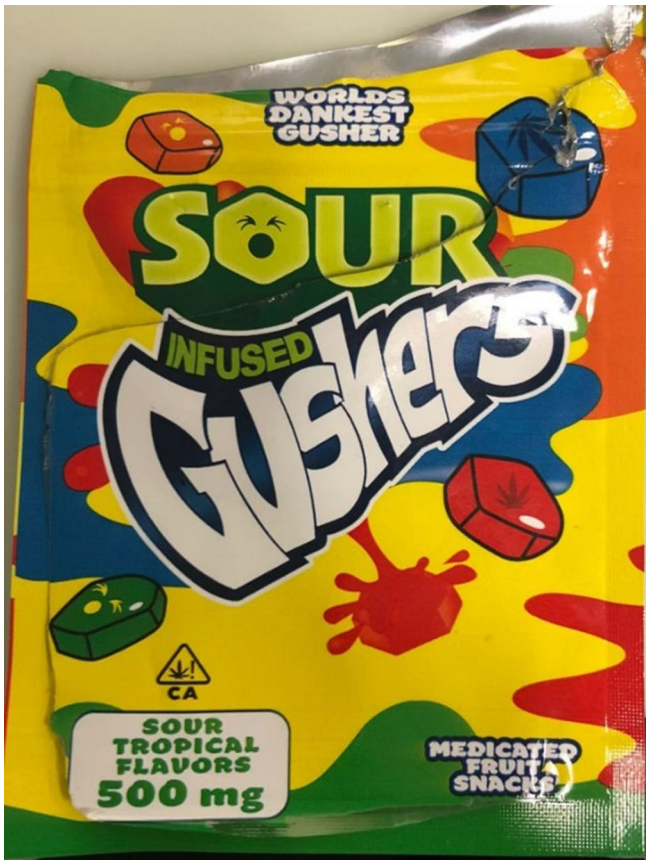

FIGURE 1 Cannabis-infused treats accidentally ingested by a young child who sought care in the emergency department for altered mental status (photo courtesy of Dr. Cara Buchanan, Los Angeles County/USC Medical Center)

3 | EPIDEMIOLOGY

The increase in legalization of marijuana has led to overall increased accessibility and exposure, especially for adolescents.[8,9] According to a National Study of Drug Use and Health in 2019, the percentage of people over age 12 years who were marijuana users within the past year increased from 25.8 million in 2002 to 48.2 million in 2019, with the number of adolescents who initiated marijuana use in the past year averaging about 3700 adolescents each day. Among adolescents 12–7 years old, this number has remained more consistent over time, with a trend toward decreased use (3.9 million users in 2002 and 3.3 million users in 2019).[7]

With the increased availability, increased use, and with packaging and presentation often mimicking candy and foods that are appealing to young children (Figures 1 and 2), there has been an increase in the number of accidental ingestions among the pediatric population. In a poison center database review of 985 inadvertent pediatric marijuana exposures, call rates in decriminalized states increased by 30% per year from 2005 to 2011, compared to no change in non-legal states.[11] A systematic review of the literature by Richards et al[12] shows that as cannabis legalization, availability, and potency increases so does the possibility of increasing unintentional pediatric cannabis intoxication and associated hospitalization.

Multiple states have decriminalized or legalized the use of marijuana for recreational use and/or legalized marijuana for medical use. These transformations appear to align with decreased perception of the drug's negative effects. Decriminalization of marijuana, which refers to removing criminal penalties and replacing them with civil penalties, such as fines and mandatory treatment, began as early as the 1970s. In addition, as early as the early 1990s, marijuana was legalized in over 33 states for medical use. In 2014, Colorado became the first state to legalize marijuana for recreational use.[4,5,13,14] These trends suggest a more normative view of marijuana in general. As legalization expands, healthcare providers will be called to care for a growing number of patients exposed to marijuana in all its forms.[11,12,14]

4 | CANNABIDIOL

4.1 | Incidence of cannabidiol overdose

As of June 30, 2021, poison control centers have managed 2158 cases in 2021 related to cannabidiol.[15] Some of these were related to additional drugs, or adulteration with a synthetic cannabinoid. Between 2017 and 2018, Utah reported 52 cases of poisoning from ingestion of CBD oil that produced symptoms that included hallucinations, nausea, vomiting, seizures, and loss of consciousness.[16] Further

FIGURE 2 Cannabis-infused sour patch kids (photo courtesy of Fiona Garlich, MD)

investigation found that this was due to a synthetic cannabinoid, 4-cyano CUMYL-BUTINACA in many of the samples.

4.2 | Clinical presentation of cannabidiol intoxication

The clinical presentation of acute CBD intoxication is usually benign, although there are occasions of inadvertent adulteration of these products with THC. Many adverse effects are gastrointestinal (nausea, emesis, diarrhea), although there are case reports of respiratory depression and psychogenic effects.[17-20] Management of cannabinoids acute overdose is mostly symptomatic.

4.3 | The lack of evidence for beneficial use in children

In contrast to adults where there is evidence supporting cannabinoids use in chemotherapy-related nausea/vomiting,[21] there is no clear evidence-based consensus on beneficial use in children. There are case reports of successful termination of refractory seizures with cannabinoids and small retrospective or observational studies.[22] The 2 large randomized controlled studies evaluating pharmaceutical-grade cannabidiol (CBD) in children with Dravet and Lennox-Gastaut syndromes demonstrated similar efficacy to other anticonvulsants.[22-24] Although the mechanism is unknown, the FDA has approved the use of a CBD drug for both Dravet and Lennox-Gastaut syndromes.[25]

4.4 | Adverse effects and management of chronic cannabidiol use

In therapeutic trials of CBD use for refractory seizures, common adverse effects included somnolence, diarrhea, decreased appetite, nausea, vomiting, and fatigue. Increase in serum alanine aminotransferase and aspartate aminotransferase were reported in up to 15% of patients, particularly in those on concurrent valproic acid treatment. Hyperammonemia and severe thrombocytopenia were also observed in some cases. All these adverse effects seemed to be dose related.[26,27] Management is discontinuation of CBD treatment. The long-term impact of CBD use is unclear. Additionally, regulation of pharmaceutical preparations may be inconsistent.

4.5 | THC incidence of acute THC overdose

In a 10-year period (2004–2014), Claudet et al[28] reported-on children less than 3 years of age admitted to a pediatric emergency department due to unintentional cannabis exposure. Twenty-nine children under the age of 3 were admitted with a positive cannabis urine test, 10 of which needed ICU-level care.[28] Eighty-seven percent of intoxications occurred at the family home. Resin was the main form of ingested cannabis (69%). The mean age was 16.5 ± 5.2 months, and mean weight was 11.1 ± 2.1 kg.[28] In a 2007–2012 data collection from a single center pediatric emergency department, Pelisser et al[29] reported on 12 toddlers (4 boys and 8 girls; mean age, 16.6 months) who had ingested cannabis, with 7 children experiencing drowsiness or hypotonia. In a more recent series, Cheng et al[30] reported on 911 poisonings reported from 2016–2018. The majority were intentional, but around 10 poisonings resulted from inadvertent ingestions by children and the median age for these was 3 years. All inadvertent ingestion occurred at home and involved cannabis belonging to the patient's family.

4.6 | Clinical presentation of THC intoxication

Clinical presentation of a patient with acute THC intoxication can vary depending on the form consumed. Pure THC in edible products can have significantly different toxic effects than unprocessed marijuana.

In children, the most common symptoms reported after acute ingestion are central nervous system depression (eg, lethargy, coma), confusion, agitation, and ataxia. Nausea and vomiting are also common symptoms of THC ingestion. More significantly, bradycardia, hypotension, seizure activity and respiratory depression requiring intubation have been reported. Other clinical effects noted include tremor, hallucinations, nystagmus, slurred speech, and muscle weakness.[11,31,32] In the Claudet et al[28] study, the majority (70%) of children suffering from neurological impairment were admitted, with 34% going to the ICU with Glasgow Coma Scala <12, and one-third of those needing assisted ventilation. There were no cases with serious lasting effects and no deaths. A similar study by Pelissa et al[29] reports a high hospitalization rate for observation, but overall favorable outcomes without established sequelae.

4.7 | Management of acute THC toxicity

Acute toxicity causes mostly central nervous system and gastrointestinal tract effects, which is typically treated supportively. There is no antidote for marijuana/THC overdoses. Symptom-based supportive care should be provided to control anxiety, vomiting, and to maintain respiratory and cardiovascular function. The majority of pediatric exposures are treated, evaluated, and released from the emergency department without aggressive treatment,[32] but prolonged coma, seizure-like activity, and other symptoms requiring ICU admission have been described.[28,31,33-35]

In a case report by Cipriani et al,[36] dexmedetomidine was found to be a fairly safe and effective medication that can be used for pediatric marijuana or natural cannabinoid exposures to aid in anxiety control. Its properties and potential to allow for "cooperative" sedation make it a more attractive choice with fewer side effects than benzodiazepines or opioids.

Managing the social aspect should also be considered. Pélissier et al[29] suggest that cannabis intoxication in children should be reported to child protection services with the aim of prevention, to detect situations of neglect and at-risk families. Although this is controversial, the authors recommend social work involvement for the safety of the child and to aid the family.

4.8 | Adverse effects and management of chronic cannabinoid use

Chronic cannabis use has been associated with various systemic and psychological effects. The most common and significant adverse effects are detailed below.

4.9 | Cannabinoid hyperemesis syndrome

Cannabinoid hyperemesis syndrome (CHS) is characterized by recurrent, paroxysmal episodes of nausea, vomiting, and abdominal discomfort in chronic cannabis users, often relieved by frequent hot bathing or showering, and followed by symptom-free periods. Young males are predominantly affected.[20,37] Multiple cases have been reported in the pediatric population.[8] The exact pathophysiology of CHS has yet to be fully elucidated, although it is postulated to involve overstimulation of enteric CB1 receptors.[37] Because of the lack of a definitive diagnostic test and its overlapping presentation with many other conditions, patients with CHS often undergo an extensive workup in the emergency department, particularly on initial presentation. Patients with CHS should be assessed and treated in the emergency department for dehydration and electrolyte abnormalities. Topical capsaicin cream 0.075%, often applied to abdomen, back, or arms, appears to be consistently efficacious for relief of CHS symptoms, although the quality of evidence supporting its use has been low.[38,39] Other potential therapies include antiemetics (eg, ondansetron, promethazine, metoclopramide, droperidol), antipsychotics (eg, olanzapine, haloperidol), benzodiazepines (eg, diazepam, lorazepam), and diphenhydramine.[12,37,40] Opioids should be avoided as much as possible.[41] Cessation of THC use is the only definitive therapy for CHS.

4.10 | Psychiatric effects

Long-term THC use has been associated with the development of psychosis and significant neuropsychiatric dysfunction.[42,43] Cannabis use in childhood is particularly detrimental as it is a period of crucial brain development and impairs acute neuropsychological functioning.[44] Cannabis use is associated with decreased intelligence quotient (IQ), and has a pronounced impact on attention, concentration, learning, memory formation, and performance. In a longitudinal study by Meier et al,[45] persistent cannabis use was associated with IQ decline, with more persistent use associated with greater decline in adolescent-onset users. Chronic use is also associated with increased depression, suicidality, anxiety, and psychosis.[46-50] Impaired psychomotor function (eg, fine motor control, reaction time) and executive function (eg, planning, reasoning, problem solving, decision making) have also been reported.[51] There appears to be a dose-dependent impact related to these negative effects. Although causation is difficult to prove, some experts believe that cannabis use during childhood is an independent causal factor in developing schizophrenia.[52,53] Cannabis use is also associated with lower educational attainment and increased use of other drugs.[54]

The evidence is conflicting regarding whether abstinence reverses these negative impacts. There is some evidence that the impact is permanent in younger developing brains.[50,55-57] Although the poor neuropsychological functioning in association with cannabis use in children has been consistently proven, the literature has been inconsistent in demonstrating the negative impact of cannabis on neuroimaging. Further studies are needed to reconcile the neuroimaging with neuropsychological test performance.[50,58,59]

Although yet unknown, neuropsychological tests may improve or recover with prolonged abstinence, as this has been observed in some studies but not others.[51,60] The age of onset of cannabis use, as well

as frequency and duration of use likely all impact recoverability. Persistent cannabis-associated impairment occurs with a dose-related impact that is more severe when cannabis is used at a young age.[57] The greater cumulative exposure and earlier age of initiations increases the likelihood of persistence cannabis-associated impairment.[57] These serious long-term sequelae are the most alarming and educational campaigns should emphasize the negative potential impact to children, young adults, and parents.

4.11 | Cardiorespiratory effects

Cannabis smoking is associated with inflammation of the airways and compromised lung function.[60,61] Adolescent cannabis users have also been found to have an increased odds ratio (5.03) of myocardial infarctions compared to non-users.[61] Cardiovascular workup (EKG, chest X-ray, laboratory tests) should be considered in the appropriate clinical settings.

4.12 | Increased potential for physical injuries

Because of altered cognitive, psychomotor, and perceptive functions, chronic THC users are at higher risk of injuries due to motor vehicle accidents, falls, or intentional self-harm.[60,61] Although most screening for THC does not specify acute versus remote use, screening for THC in patients with presentations concerning for intoxication may be warranted to assess for future risk.

4.13 | Adverse effects in utero

Cannabis use during pregnancy has been associated with neurodevelopmental disorders and autism spectrum disorders of infants (born to mothers who used while pregnant).[62]

4.14 | Withdrawal from THC

According to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, cannabis withdrawal syndrome is defined by the presence of at least 3 of the following symptoms developing within 7 days of reduced cannabis use in the setting of daily usage over several months: (1) irritability, anger, or aggression; (2) nervousness or anxiety; (3) sleep disturbance; (4) appetite or weight disturbance; (5) restlessness; (6) depressed mood; and (7) somatic symptoms, such as headaches, sweating, nausea, vomiting, or abdominal pain.[63] Most symptoms appear 24–72 hours after cessation of use and reach peak intensity over the first week. Withdrawal symptoms may sometimes last several weeks or months after cessation of use due to the highly lipophilic nature of THC and its metabolites, hence their extended half-lives. In a study by Greene and Kelly on adolescents in an outpatient treatment program, withdrawal symptoms were reported by 40% of the participants who used cannabis.[64] Treatment includes behavioral therapy and a variety of pharmacologic agents (dronabinol, nabiximols, gabapentin, quetiapine, sedatives, and hypnotics).[65] To date no study has been published on cannabis withdrawal syndrome treatment in the emergency department setting.

4.15 | Combating cannabis use in children

Cannabis acceptance has increased since legalization as has its use and perception of safety or lack of adverse outcomes.[66] The evidence is clear that this belief is untrue. Except for some refractory epilepsy and seizure disorders, there is no established beneficial use of cannabis in children. Contrast this with extensive evidence for serious, permanent harm on developing brains leads to concern and a call for intervention. There is room for optimism though. High parental monitoring and negative peer attitudes toward cannabis use act as protective factors against cannabis use. In a study by Mariani et al,[67] those children who perceived that their peers disapproved of cannabis use, believed that cannabis use was risky, and that school was important were less likely to use. Active involvement in extracurricular activities was also protective.

5 | CONCLUSION

This informational paper summarizes the current literature on cannabis in children, including incidence, short- and long-term effects and uses. The perception that marijuana is "safe" appears to be driven, in part, by legalization. The use of marijuana and cannabinoid products in general is not without harm, particularly in children, and the incidence of permanent neuropsychiatric sequelae demands action and increased preventative education.

Physicians, parents, peers, and individuals must be informed and rise to the challenge of addressing and opposing misinformation and untrue perceptions. Collectively, we need to work to improve the health of our children and protect future generations. The current trend of increasing marijuana use and availability will negatively impact the physical and mental health of children. Additionally, cannabis use impacts their ambition, achievement, and productivity. Ultimately, cannabis use in children will negatively impact their future. It is important that this information is communicated to this generation for their health, happiness, and productivity.

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CONFLICTS OF INTEREST

The other authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

All authors contributed to the concept, design, and writing of this publication.

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